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(21) International Application Number: PCT/EP95/01463 (22) International Filing Date: 19 April 1995 (19.04.95) (30) Priority Data: 9408117.1 23 April 1994 (23.04.94) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19103 (US). (71) Applicant (for MG only): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): CONLEY, Creighton, Pierce [US/US]; SmithKline Beecham Pharmaceuticals, Bristol Industrial Park, Weaver Pike, Bristol, TN 37620 (US). DAVIDSON, Nigel, Philip, McCreath [GB/US]; SmithKline Beecham Pharmaceuticals, Bristol Industrial Park, Weaver Pike, Bristol, TN 37620 (US). (74) Agent: WALKER, Ralph, Francis; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: POLYMER COATED TABLET COMPRISING AMOXYCILLIN AND CLAVULANATE		
(57) Abstract <p>A tablet formulation, being a medicament for oral administration for the treatment of bacterial infections, the tablet comprising a compacted mixture of 750-950 mg of amoxycillin and a quantity of clavulanate in a weight ratio amoxycillin:clavulanate between 6:1 to 8:1 inclusive, and having a film coating of polymers which can be applied by aqueous film coating techniques.</p>		

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Polymer coated tablet comprising amoxycillin and clavulanate

5 The present invention relates to medicaments for oral administration in the treatment of bacterial infections, comprising amoxycillin and salts of clavulanic acid.

Amoxycillin and its derivatives, e.g. amoxycillin trihydrate, are known (e.g. GB 1241844) as antibacterial agents useful in the treatment of gram-negative and gram-positive bacterial infections. Clavulanic acid and its derivatives, e.g. its salts such as potassium clavulanate, are known (e.g. GB 1508977) as β -lactamase inhibitors which inhibit the activity of β -lactamase enzymes produced by bacteria and which confer antibiotic resistance by destroying β -lactam antibiotics such as amoxycillin. The terms "amoxycillin" and "clavulanate" used herein unless otherwise specified include both the free parent acids and derivatives such as salts thereof. The use of clavulanate in combination with amoxycillin consequently enhances the effectiveness of amoxycillin.

The use of potassium clavulanate in combination with amoxycillin trihydrate within the ratios amoxycillin: clavulanic acid 1:1 to 6:1, (expressed in terms of the weight of parent compound amoxycillin or clavulanic acid, this terminology being used throughout this description unless otherwise stated) is described in GB 2005538. Potassium clavulanate is an exceptionally difficult material to formulate, being extremely hygroscopic and moisture sensitive. Degradation readily occurs in the presence of water and aqueous media.

Known formulations of amoxycillin and clavulanate are provided for administration three times daily (i.e. "tid" dosing). It is desirable for *inter alia* patient convenience and compliance that such formulations be provided for administration twice daily (i.e. "bd" dosing). It is also highly desirable that such formulations should have a consistent bioavailability of the active ingredients clavulanate and amoxycillin.

An amoxycillin/clavulanate formulation has been produced which enables bd dosage, and also has the unexpected benefit of a particularly consistent bioavailability, particularly of clavulanate. In some instances the formulation may also show a increased bioavailability.

Accordingly the present invention provides a tablet formulation, being a medicament for oral administration for the treatment of bacterial infections, the tablet comprising a compacted mixture of 750-950 mg of amoxycillin and a quantity of clavulanate, in a weight ratio amoxycillin : clavulanate between 6:1 to 8:1 inclusive, and having a film coating of polymers which can be applied by aqueous film coating techniques.

Suitable derivatives of amoxycillin are amoxycillin trihydrate, anhydrous amoxycillin and alkali metal salts of amoxycillin such as sodium amoxycillin. Suitable derivatives of clavulanic acid are alkali metal salts of clavulanic acid such as potassium clavulanate. It is preferred to use amoxycillin trihydrate and potassium clavulanate in combination in a tablet formulation of this invention containing the two, this combination having met with regulatory approval, and being particularly advantageous.

Suitably the tablet contains nominally 875 mg of amoxycillin $\pm 10\%$ and 125 mg of clavulanate $\pm 10\%$, i.e. in a ratio amoxycillin : clavulanate of nominally 7 : 1. The tablet of the invention may suitably contain 50 wt. % or more, for example around 65-75 wt. % of the combination of amoxycillin and clavulanate, e.g. typically 70 wt. % ± 2 wt. %.

The tablet formulation of this invention may be provided for treatment of bacterial infections generally, for example one or more of *inter alia* upper respiratory tract infections, lower respiratory tract infections, genito- urinary tract infections and skin and soft tissue infections. The tablet formulation of this invention is generally suitable for treatment of infections by microorganisms which are susceptible to β -lactam antibiotics, and may also have efficacy for some penicillin-resistant microorganisms.

The tablet formulation of the invention may include one or more other additional excipients etc. generally conventional to the dosage form in question. For example tablet dosage forms may contain one or more conventional diluents such as microcrystalline cellulose (which can also function as a compression aid) e.g. comprising around 20-35 wt % of the tablet e.g. 25-30 wt %; disintegrants such as sodium starch glycolate, e.g. comprising 0.5-3.5 wt % of the tablet e.g. 1.75-2.25 wt %; lubricants such as magnesium stearate e.g. comprising 0.5-1.5 wt % of the tablet e.g. 0.75-1.25 wt % and glidants, such as colloidal silicon dioxide, e.g. comprising 0.25-1.0 wt % of the tablet e.g. 0.5-0.9 wt %. Although the above-listed classes and examples of excipients, together with the active ingredients may make up the 100% uncoated core weight of the tablet, in addition the tablet forms may contain flavouring agents, colourants, preservatives, desiccants etc. conventional to the dosage form in question up to the 100% uncoated core weight of the tablet.

Tablets of the invention may be made by conventional tablet manufacturing techniques, e.g. blending of the ingredients followed by dry compaction, granulation then compaction of the granulate to form the compacted tablet core. A suitable granulate may be produced for example by slugging or roller compaction.

Roller compaction generally involves a screening procedure that can lead to a narrower particle size distribution with fewer particles at either extreme of the

size range. Roller compaction may also be better suited to large scale and continuous of the granulate from which the tablet of the invention is formed, because although pharmaceutically slugging and roller compaction are generally considered as entirely equivalent, in the tablet of the invention roller compaction is found to contribute to an unexpected increase in consistency of bioavailability and is hence preferred. A suitable method of roller compaction is via use of the known "Chilsonator" roller compactor. A description of such a roller compactor is included in for example "The Theory and Practice of Industrial Pharmacy" Lachan et al. 3rd Edn. Lea & Febiger (1986) page 318-320. It is also preferred that the preparation of the formulations of the invention is carried out under conditions of low humidity, e.g. less than 30% RH, more suitably less than 20% RH, ideally as low as possible, to assist in preservation of the highly moisture sensitive clavulanate, particularly potassium clavulanate.

Polymers which can be applied by aqueous film coating may facilitate application of the film coating by aqueous film coating techniques, thereby avoiding the need for organic solvents. Suitable polymers include hydroxypropylcellulose, hydroxypropylmethyl cellulose, ethylcellulose (for example ethylcellulose in a latex composition as supplied by the FMC Corporation as "Aqua-Coat" (trade mark)), methylhydroxyethylcellulose, polyvinylpyrrolidone ("PVP", e.g. as supplied under the name Povidone (trade mark), sodium carboxymethylcellulose and acrylate polymers (e.g. the known methacrylic acid esters supplied under the trade name "Eudragit" (trade mark)).

A preferred polymer is hydroxypropylmethylcellulose ("HPMC") suitably in combination with a polyethylene glycol ("PEG"). PEG's of low molecular weight (200 to 600 series) are liquid at room temperature and find use as plasticisers. PEG's with high molecular weights (900 to 8000) are waxy solids at room temperature and are used in combination with low molecular weight PEG's and with other polymers such as HPMC to modify film properties and to contribute to tablet sheen.

A preferred polymer which can be applied by aqueous film coating techniques is one or more hydroxypropylmethyl celluloses combined with one or more PEG's. HPMC polymers have the advantages of solubility in physiological fluids as well as water, non-interference with tablet disintegration, dissolubility or drug availability, formation of a flexible film, freedom from objectionable taste or odour, stability to heat, light, air, moisture, compatibility to stabilisers, colourants opacifiers, and gloss. The hydroxypropylmethylcellulose functions as a film former, and the polyethylene glycol functions as a plasticiser. The hydroxypropylmethyl cellulose: polyethylene glycol ratio in the film coating is suitably between 7.5 : 1 to 5.5 : 1, e.g. around 6.5 : 1 $\pm 10\%$. Suitably the

hydroxypropylmethyl cellulose is applied in the form of a mixture of hydroxypropylmethyl cellulose 6 cps and 15 cps, in a ratio of around 2:1 to 4:1 e.g. around 3:1 $\pm 10\%$. Suitably the polyethylene glycol is applied in the form of a mixture of polyethylene glycol 4000* and 6000* in a ratio between around 1:2 to 2 : 1, e.g. around 1 : 1 (* in the USA these materials are supplied as polyethylene glycol 3350 and 6000* respectively). The film coat may also suitably include an opacifier, for example titanium dioxide (white). Suitably the opacifier may be present in around a 1:1 $\pm 10\%$ proportion with the hydroxypropylmethyl cellulose in the film coat.

10 The materials of the film coat are preferably applied by an aqueous film coating process, as application in this way form a film of a nature which also appears to contribute to the improved consistency in bioavailability. A suitable solids loading for the aqueous film coat is around 10-30% w/v, typically 10-20%, e.g. 15% $\pm 2\%$.

15 Suitably the film coating is applied so as to deposit a weight of dried film materials corresponding to around 1.0 - 4.0 wt. % of the total coated tablet weight.

Preferably the dosage forms of the medicament of the invention are packaged in a container that inhibits the ingress of atmospheric moisture, e.g. blister packs or tightly closeable bottles etc. as conventional in the art. Preferably bottles also include a desiccant material to preserve the clavulanate.

20 The unit dosage form(s) of the medicament of the invention may suitably be for oral administration, for example at intervals separated by 6 or more hours, e.g. separated by 8 or more hours, e.g. separated by up to around 12 hours. Although particularly suited to bd dosing, the tablet formulation of this invention may also be administered at a greater frequency e.g. tid dosing, for appropriate indications and within approved dosing limits.

25 Suitable total daily dosages of amoxycillin are in the range 900 - 1800 mg daily, preferably 1000 - 1750 mg inclusive daily. Suitable total daily dosages of clavulanic acid are in the range 200 - 300 mg daily, preferably 250 ± 10 mg inclusive daily. Within the total daily dosages referred to above, for oral administration bd, the tablet of the invention may be orally administered at intervals separated by around 8 - 12 hours.

35 The invention further provides a method of treatment of bacterial infections in human beings or in animals comprising the oral administration to a human being or animal in need of such treatment of a medicament as described above not more than twice a day.

The invention also provides a method for the preparation of a tablet formulation, being a medicament for oral administration for the treatment of bacterial infections, which comprises compacting a mixture of 750-950 mg of

amoxycillin and a quantity of clavulanate, in a weight ratio amoxycillin: clavulanate between 6:1 and 8:1 inclusive, and coating the compact with a film coating which comprises hydroxypropylmethyl celluloses and polyethylene glycols.

Suitable and preferred forms of this process are as described above with
5 reference to the tablet formulation itself *mutates mutandis*.

The invention also provides a tablet formulation as described above for use as an active therapeutic substance.

The invention also provides a tablet formulation as described above for use in the treatment of bacterial infections.

10 The invention also provides the use of a tablet formulation as described above in the manufacture of medicament for use in the treatment of bacterial infections.

The invention also provides a method of treating a bacterial infection in a human patient which includes the step of administering an effective amount of
15 amoxycillin and clavulanate comprised in a tablet formulation as described above.

The invention will now be described by way of example only.

Example 1.

A tablet formulation was prepared having the following composition:

Ingredient	(mg.)	wt. %	Function	Ref.to Std.
Active Constituents¹:				
Amoxicillin trihydrate	1017.4	70.2	Active ingdt.	EP
(equivalent to amoxicillin)	875.00			
Potassium clavulanate	152.45	10.5	Active ingdt.	G319
(equivalent to clavulanic acid)	125.0			
Other Constituents:				
Magnesium Stearate	14.50	1.00	Lubricant	NF
Sodium Starch Glycollate	29.00	2.00	Disintegrant	NF
Colloidal Silicon Dioxide	10.0	0.70	Glidant	NF
Microcrystalline Cellulose	226.65	15.6	Compression aid & Diluent	NF
Core tablet weight	1450.00	100.00		
Film Coat²				
Purified Water	NA	NA	Solvent	USP
Opadry White YS-1-7700	32.0	2.2	Film Coat	NA
Opadry White YS-1-7700 can be broken down as below:				
Titanium Dioxide	13.76	43.0	Opacifier	EP
Hydroxypropylmethyl cellulose 6cps	10.56	33.0	Film Former	
Hydroxypropylmethyl cellulose 15 cps	3.52	11.0	Film Former	JP
Polyethylene Glycol 3350 ³	2.08	6.5	Plasticizer	USNF
Polyethylene Glycol 8000 ³	2.08	6.5	Plasticizer	USNF XVII
Purified Water ⁴	NA	NA	Solvent ⁴	USP
Nominal coated tablet weight:	1482.00			

¹These amounts are dependent upon the potencies of the actives used and are based on 86% for amoxicillin and 82% for potassium clavulanate (clavulanate potassium 41% is part of a 1:1 blend with microcrystalline cellulose). Constant tablet weight is

maintained through adjustment of the quantity of microcrystalline cellulose according to the potency of the actives.

2The Film coat constituents may be supplied as a dry powder blender either, ex Colorcon, as Opadry White YS-1-7700 in the USA or Opadry White OY-S-7300 in Europe. Wt.% for film coat constituents are expressed as a percentage of the Opadry film weight.

3Polyethylene Glycols 3350 and 8000 are supplied in Europe as Polyethylene Glycols 4000 and 6000 respectively.

4The Purified Water is removed during processing.

10 The Film Coat is applied to 100% of the core weight.

The tablets were made by blending the amoxycillin, potassium clavulanate, and portions of microcrystalline cellulose and magnesium stearate, roller compacting (chilsonating) this blend, then blending with the other constituents, before tableting on a conventional tablet press and coating. The process is described in more detail below.

All components are sifted or charged to the blender through a vibratory feeder equipped with a 4 mesh screen or through a 14 mesh blender screen, and through a mill unless otherwise noted. The mill is operated at 1500 rpm, knives forward, with a 0.093 inch perforated plate.

20 An approximately 2/3 portion of the microcrystalline cellulose is loaded into a suitable blender. An approximately 1/5 portion of the amoxycillin trihydrate is loaded into the blender. Half of the magnesium stearate is loaded through a 14 mesh screen into the blender. The mix is blended for two minutes. Another 2/5 portion of amoxycillin trihydrate and 1/2 of the potassium clavulanate / microcrystalline
25 cellulose blend is loaded into the blender. The mix is blended for three minutes. The remainder of the amoxycillin trihydrate and of the potassium clavulanate / microcrystalline cellulose blend is then loaded into the blender. The mix is blended for five minutes.

The blended contents are passed through a Chilsonator of appropriate capacity, under a pressure of 1000 psi, then discharged through a Fitzmill operating at 1800 rpm, knives forward, with a 0.079" - 0.109" perforated plate, followed by screening over a vibrascreen fitted with an upper screen of 14 mesh and a lower screen of 18 mesh, recycling and recompacting the over- and under- sized granulation until the acceptable sieve cut is 98% of the load.

35 Approximately a 10% portion of the granulation is loaded into the blender, bypassing the mill. The colloidal silicon dioxide, sodium starch glycollate and remaining portions of magnesium stearate and microcrystalline cellulose are loaded into the blender, and the mix is blended for five minutes. The remaining granulation is loaded into the mixer, by-passing the mill, and blended for 15 minutes.

The blend is compressed, using a suitable tablet press fitted with 0.3937" x 0.8465" capsule shaped punches, to form tablets having a weight of 1.450 g with hardness and thickness values within manufacturing guidelines for pharmaceutical tablets.

- 5 The tablet cores are then coated with the aqueous film coat at a 300Kg batch size in a 60" (150 cm) coating pan. The preferred coating process requires dehumidified inlet air at a sufficient temperature that can produce a relative exhaust humidity of less than 12% during the spraying operation.

- 10 In a clinical trial the tablet of Example 1 showed a decreased inter subject variability. Although specifically exemplified by the tablet of Example 1, this effect may also be observed with pharmaceutically equivalent tablets having a composition in which the proportions of ingredients differ within for example + 10%, e.g. +5% of the values given in Example 1.

Claims:

1. A tablet formulation, being a medicament for oral administration for the treatment of bacterial infections, the tablet comprising a compacted mixture of 750-
5 950 mg of amoxycillin and a quantity of clavulanate in a weight ratio amoxycillin : clavulanate between 6:1 to 8:1 inclusive, and having a film coating of polymers which can be applied by aqueous film coating techniques.
2. A tablet formulation according to claim 1 characterised in that the
10 amoxycillin is in the form of amoxycillin trihydrate and the clavulanate is in the form of potassium clavulanate.
3. A tablet formulation according to claim 1 or 2 characterised in that the tablet
15 contains 875 mg of amoxycillin $\pm 10\%$ and 125 mg of clavulanate $\pm 10\%$, i.e. in a ratio amoxycillin : clavulanate of nominally 7 : 1.
4. A tablet formulation according to claim 1, 2 or 3 additionally containing microcrystalline cellulose comprising 20-35 wt % of the tablet; sodium starch glycolate comprising 0.5-3.5 wt % of the tablet; magnesium stearate comprising
20 0.5-1.5 wt % of the tablet; colloidal silicon dioxide comprising 0.25-1.0 wt % of the tablet; together with the active ingredients making up the 100% uncoated core weight of the tablet.
5. A tablet formulation according to any one of claims 1 to 4 characterised in
25 that the formulation is made by compaction of a granulate prepared by roller compaction
6. A tablet formulation according to any one of claims 1 to 5 characterised in that the film coating comprises hydroxypropylcellulose, hydroxypropylmethyl
30 cellulose, ethylcellulose, methylhydroxyethylcellulose, polyvinylpyrrolidone, sodium carboxymethylcellulose or acrylate polymers.
7. A tablet formulation according to claim 6 characterised in that the film
35 coating comprises hydroxypropylmethylcellulose in combination with a polyethylene glycol.
8. A tablet formulation according to claim 7 characterised in that the hydroxypropylmethyl cellulose: polyethylene glycol ratio in the film coating is between 7.5 : 1 to 5.5 : 1.

9. A tablet formulation according to claim 8 characterised in that the polyethylene glycol is applied in the form of a mixture of polyethylene glycol 4000* and 6000* in a ratio between 1:2 to 2:1 (* in the USA these materials are supplied as polyethylene glycol 3350 and 6000* respectively).
10. A tablet formulation according to any one of the preceding claims characterised in that the weight of dried film materials corresponds to around 1.0 - 4.0 wt. % of the total coated tablet weight.
11. A tablet formulation according to any one of the preceding claims substantially as hereinbefore described with reference to Example 1.
12. A method of treatment of bacterial infections in human beings or in animals comprising the oral administration to a human being or animal in need of such treatment of a medicament according to any one of claims 1 to 11 not more than twice a day.
13. A method for the preparation of a tablet formulation, being a medicament for oral administration for the treatment of bacterial infections, which comprises compacting a mixture of 750-950 mg of amoxycillin and a quantity of clavulanate, in a weight ratio amoxycillin: clavulanate between 6:1 and 8:1 inclusive, and coating the compact with a film coating which comprises hydroxypropylmethyl celluloses and polyethylene glycols.
14. A tablet formulation according to any one of claims 1 to 11 for use as an active therapeutic substance.
15. A tablet formulation according to any one of claims 1 to 11 for use in the treatment of bacterial infections.
16. The use of a tablet formulation according to any one of claims 1 to 11 in the manufacture of medicament for use in the treatment of bacterial infections.
17. A method of treating a bacterial infection in a human patient which includes the step of administering an effective amount of amoxycillin and clavulanate comprised in a tablet formulation according to any one of claims 1 to 11.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 95/01463

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/43 A61K31/42 A61K9/20 A61K9/28 A61K47/00
 //(A61K31/43,31:42)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 441 609 (CROWLEY PATRICK J) 10 April 1984	1,2,6, 14-16
Y	see claim 1 and example 9 "	2-10,13

X	US,A,4 537 887 (ROOKE DAVID J ET AL) 27 August 1985	1,2,6, 14-16
	See Claims 1, 2 and 5; col. 2, l. 52-58	
Y	"	3-5,7,8, 13

X	US,A,4 232 005 (HOWARTH THOMAS T) 4 November 1980	1,14-16
Y	See claims 1, 6, 7 and 12 "	2-10

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

1 August 1995

Date of mailing of the international search report

14.08.95

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 95/01463

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP,A,0 080 862 (BEECHAM GROUP PLC) 8 June 1983 see the whole document -----</p>	<p>1-10, 13-16</p>

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 95/01463

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4441609	10-04-84	AU-B- 525089	21-10-82
		AU-A- 4050678	17-04-80
		BE-A- 870988	03-04-79
		CA-A- 1105385	21-07-81
		CH-A- 642258	13-04-84
		DE-A- 2843318	12-04-79
		FR-A,B 2405711	11-05-79
		GB-A,B 2005538	25-04-79
		JP-C- 1494273	20-04-89
		JP-A- 54076831	19-06-79
		JP-B- 63041886	19-08-88
		NL-A,B 7810176	17-04-79
		SE-B- 435899	29-10-84
		SE-A- 7810591	11-04-79
		SE-B- 451668	26-10-87
		SE-A- 8107592	17-12-81
		US-A- 4301149	17-11-81
US-A-4537887	27-08-85	AU-B- 549321	23-01-86
		AU-A- 7568481	08-04-82
		CA-A- 1187796	28-05-85
		EP-A,B 0049061	07-04-82
		GB-A,B 2084016	07-04-82
		JP-B- 1055244	22-11-89
		JP-C- 1568566	10-07-90
US-A-4232005	04-11-80	JP-A- 57091921	08-06-82
		GB-A- 1545467	10-05-79
		AT-B- 342199	28-03-78
		AU-B- 497577	21-12-78
		AU-A- 1302076	20-10-77
		BE-A- 840253	30-09-76
		CA-A- 1074802	01-04-80
		CH-A- 602742	31-07-78
		DE-A- 2616088	28-10-76
		FR-A,B 2336130	22-07-77
		JP-A- 51127093	05-11-76
		LU-A- 74749	11-11-76
		NL-A- 7603840	18-10-76
		SE-B- 427037	28-02-83

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 95/01463

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4232005		SE-A- 7604287	15-10-76
		US-A- 4297345	27-10-81
		US-A- 4428937	31-01-84
		US-A- 4098897	04-07-78
<hr/>			
EP-A-0080862	08-06-83	AU-A- 9103782	09-06-83
		JP-C- 1580055	13-09-90
		JP-B- 2006332	08-02-90
		JP-A- 58109419	29-06-83
<hr/>			